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TOPIC :

THE IMPACT OF EXERCISE TRAINING ON ENDOTHELIAL FUNCTION IN HEART FAILURE PATIENTS: A SYSTEMATIC REVIEW.

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SYTEMATIC REVIEW

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LIST OF TABLES AND FIGURES

List of abbreviations

AIT…… Aerobic interval training

ACEi…… Angiotensin converting enzyme inhibitor

ARB……. Angiotensin receptor blocker

ART…… Aerobic resistance training

AT……. Aerobic training

AHA…….. American Heart Assosiation

BACPR……... British Assosiation of Cardiovascular Prevention and Rehabiltation

CHF…… Congestive heart failure

CAD…… Coronary artery disease

CRT……..... Cardiac resynchronization therapy

CBT ……. Cognitive behavioural therapy

CRP…… Cardiac rehabilitation programme

CVD…….. Cardiovascular disease

C-ET……. Conventional exercise training

EF…….. Endothelial function

Ef ……. Ejection fraction

ET…….. Exercise training

FBF…… Forearm blood flow

FMD…….. Flow-mediated dilation

HF…….. Heart failure

HRmax……... Maximum heart rate

HFPEF…….. Hear failure with preserved ejection fraction

HFREF…….. Heart failure with reduced ejection fraction

ICD…… Implantable cardioverter defibrillator

IHD…….Ischemic heart disease

ICAM…….Intracellular adhesion molecule

IL……Interleukins

L-arg……. L-arginine

LV……..Left ventricule

LVEF…….Left ventricular ejection fraction

MET……. Metabolic equivalent

MI……..Myocardial infarction

MACG……...Machine-assisted cycling group

MCT……..Moderate continuous training

NICE……..The National institute for health and care excellence

NYHA……New York Heart Association

NHFA…….National Heart Failure Audit

NO……..Nitric oxide

PECAM……..Platelet/endothelial cell ahesion molecule

RAAS……..Renin-angiotensin-aldosterone system

RC……...Healthy subjects

RH-PAT…… .Reactive Hyperaemia Peripheral Arterial Tonometry

RCT…….Randomized Control Trial

SRT…….Steep ramp test

TNF……Tumour necrosis factor

TPR……Total peripheral resistance

VCAM……Vascular cell adhesion molecule

LITERATURE REVIEW

1.0 INTRODUCTION

1.1 HEART FAILURE

Heart failure (HF) is a chronic disease with debilitating consequences which has become a threat to the global health care system. The American Heart Assosiation (AHA) reported the prevalence of HF in its population as 2.6% as of 2006 with more than 200,000 deaths linked to it. Following improved standard of living and increasing aging population, this entity has risen dramatically in the developed countries. Approximately 550,000 people are diagnosed with HF annually in the United State and this number is expected to rise to 1.5 million by 2040 (Asrar, Goy, Levinger, Wong & Hare, 2015). It is estimated that about 17 – 45% of patients admitted in the hospital with HF do not survive beyond one year post-admission while majority die within 5 years of admission. However, the survival rate for HF have increased in most parts of the world and this has been attributed to the improvement in medical care and evidenced-based treatment methods (Ponikowski *et al.* 2014). In the UK, in-hospital mortality has fallen from 11.1% in 2011 to 9.4% in 2013; which corresponds to a relative and absolute reduction of 15.3% and 1.7% respectively. In addition, mortality for those admitted in the hospital with HF who survive until discharge has also reduced significantly from the year 2011 to 2013 (National Heart Failure Audit (NHFA), 2012). Although significant progress has been made, yet about 2 – 17% of patients admitted to the hospital with HF die during hospitalisation while those who have less symptoms and are treated on out-patient's basis seem to have better prognosis. The basis for this disparity still remains unclear and the best therapeutic intervention so far offered to HF patients only provide symptomatic relieve but no real change in terms of modifying disease progression or final outcome. Despite obvious improvement in care over the past 20 years, HF has remained a threat to public health and its poor survival rate makes it even worse than breast, bowel or even prostate cancer. Nearly 26 million people are living with HF prompting some to refer to it as a global pandemic. In North America and Europe, less than 20% of the patients with HF are 50 years or under whereas more than 80% of them are 65year or above; and the number is thought to be on the increase in countries with ageing population (Ponikowski *et al*. 2014).

Exercise training (ET) has been well established as an adjunct therapy in the management of HF. Prior to three decades ago, exercise was prohibited for HF patients while bed rest was rather recommended. However, this line of thought has since been challenged and the first evidence was published in 1990 arguing in favour of exercise training which showed that exercise tolerance and HF symptoms improved following exercise without any adverse outcome (Asrar Ul Haq, Goy, Levinger, Wong & Hare, 2015).

The aim of this review therefore is to examine:

(1) The basic clinical science about the heart and circulation
(2) Heart failure: causes and management
(3) Different modes of exercise before proceeding to its benefits in terms of correction of endothelial dysfunction in these group of patients.

2.0 CARDIAC ANATOMY

2.1 LAYERS OF THE HEART WALL

The wall of the heart is made up of three layers: epicardium, the myocardium and the endocardium. The epicardium is the outer most part of the heart and is synnonymous with the serous pericardium and can become fatty in the elderly. The middle layer known as the myocardium forms the muscular part of the heart. It is the layer that contracts during cardiac cycle. Crisscrossing connective tissue fibres link muscles cells to each other in this layer forming spiral or circular bundles which connect all the parts of the heart together. These connective tissue form a fibrous skeleton for the heart which helps to reinforce the myocardial cells providing strenght internally. This connective tissues (collagen and elastic fibres) are thicker in some parts of the heart. There absence means that the great vessels and valves would be stretched to their maximum and might eventually be worn out due to the enormous amount of stress that is exerted on them during each blood cycle. Third layer is the endocardium, which is the squamous epithelium lining the inner surface of the heart chambers and provides cover to the fibrous skeleton of the heart valves. This endocardium is continous with the endothelium of the peripheral vasculature (Marieb & Hoehn, 2010).

2.2 HEART CHAMBERS

The heart consist of four chambers: two receiving chambers (atria) and two discharging chambers (ventricules). The atria are made up of the auricles and the right and left atria. Internally the right atrium has a smooth-walled posterior part and an anterior with irregular bundle end known as pectinate muscle. The anterior and posterior parts are demarcted by a semi-circular rigde (crista terminalis). Conversely, the left atrium is mostly smooth and the pectinate muscle are located only on the auricle. The interatrial septum has a slight depression, the fossa ovalis, which is an embyonic remnant of fetal circulation. The atria are thin walled since they do minimal work of pushing the blood down the gradient. Basically, blood enters the right atrium from the coronary sinus, superior and inferior vena cava. While the left atrium recieves blood from the four pulmonary veins.

The ventricles primarily make up the greater volume of the heart. The right ventricle form the major part of the anterior surface of the heart whereas the left ventricle occupies most of the posterior and inferior surface. The trabeculae carnea mark the internal surface of the ventricles with the papillary muscles which play a vital role in valve closure during systole. The ventricles are responsible for pumping blood out of the heart, as a result, their walls are thicker in size. The right ventricle pumps blood into the pulmonary bed where gaseous exchange takes place while the left ventricles pump blood directly through the aorta into the systemic circulation(Marieb & Hoehn, 2010).

2.3 CARDIAC FUNCTION

Research has shown that heart functions are directly linked to the atrial pressures. This pressure can be plotted as an independent variable against other markers of cardiac function. Four types of function curves have been use in describing cardiac function but the curve relating cardiac output to mean right atrial pressure appears most useful in describing heart function. This curve indicate a significant rise in cardiac output with a slight increase in right atrial pressure. This perculiarity in essense, is as a result of stretch on the cardiac muscle fibre. As the end diastolic pressure increases, the ventricular volume expands, lengthening the cardiac muscle fibres. Following this, the force of contraction of the fibres increases, giving rise to enormous amount of pumping ability in the ventricules. This effect was described nearly hundred years ago by starling and his colleagues and is known as starling's law of the heart.

This intrinsic ability of the heart enables it to double its output with a single contraction when the end diastolic contraction is raise by 1 or 2 mmHg. However, the heart reaches its elastic limit when the fibre are stretch to a maximum. The mean ventricular end diastolic pressure at which the cardiac output flattens out on the curve is the filling pressure that yields the greatest amount of force from the ventricules. Systemic resistance and arterial pressure affects the cardiac function curve. If the resistive load is held at a constant then arterial pressure will gradually increase as cardiac output increase; as a result the pumping ability of the left ventricule will be reduced as more force required to overcome the ongoing resistance (Young, 2010).

3.0 VASCULAR ANATOMY & PHYSIOLOGY

In terms of function, the tunica intima together with the vascular endothelium and the tuinca media (which contains smooth-muscle cells) make up the blood vessels. They are linked in specific ways to maintain the vascular tone.Blood vessel tone is controlled centrally with the sympathetic and parasympathetic nervous system. Equally, endocrine actions also occur. When neural component is damaged, for example, in pathological state, then the endocrine control of blood vessels mediates using adrenaline, angiotensin or vasopressin. In the event of arterial blood pressure instability, blood vessels vasoconstrict independently of nervous input when blood pressure drops and vice versa. This process of autoregulation is a direct result of the blood vessels' ability to constrict when distended (bayliss myogenic response) and that caused by reduced amount of tissue metabolite (vasodilator washout). The vascular endothelium is a cardiovascular endocrine organ, and interfaces between blood and other tisues. It produces various compounds as listed below :

Table 1. **MAJOR ENDOTHELIAL PRODUCTS AND FUNCTIONS**

Endothelial product	Function(s)	stimulus
Nitric oxide	Vasodilatation Inhibits platelet aggregation Inhibits transcription of adhesion Molecules Inhibits vascular smooth muscle proliferation	Shear stress, e.g. induced by exercise Agonists: thrombin, acetylcholine, Endothelin, bradykinin, serotonin, substance P, inflammation/endotoxin shock
Prostacyclin (PG1)	Vasodilatation Inhibits platelet aggregation	Agonist: thrombin inflammation
Prostanoids	Vasoconstriction	hypoxia
Endothelin	Vasoconstriction	Thrombin, angiotensin II, vasopressin Hypoxia Note: inhibited by shear stress
Endothelial-derived Hyperpolarizing factor	Vasodilatation	Agonist: bradykinin, acetylcholine
Angiotensin-converting enzyme	Vasoconstriction	Expressed naturally
Von willebrand factor	Promotes platelet aggregation Stabilizes factor VIII	Agonist: thrombin, epinephrine
Adhesion molecules P,L,E selectins ICAM, VCAM, PECAM	Marginating of white blood cells Binding and diapedesis of WBCs into Vessel wall	Inflammatory mediators: histamine, thrombin, TNF, IL-6
Vascular endothelial growth factor (VEGF)	Angiogenesis Vasodilatation Increased vascular permeability	Pregnancy Hypoxia Inflammation, e.g. rheumatoid arthritis Trauma

ICAM, intracellular adhesion molecule; VCAM, vascular cell adhesion molecule, PECAM, platelet/endothelial cell adhesion molecule; TNF, tumour necrosis factor; IL, interleukin

(kumar & Clark, 2012)

4.0 HEART FAILURE

4.1 DEFINITION

Heart failure(HF) is a complex clinical syndrome of signs and symptoms suggesting an impairment in the ability of the heart to function as a pump to support the circulatory system. It is often as a result of structural or functional abnormalities in the heart (NICE, 2010). This condition affects approximately 5.7 million people globally and those with HF experiences great reduction in the quality of their life in addition to frequent hospital admissions. Patients with HF presents with different symptoms, some of which develop insidiously over many days whereas in other circumstance, it could develop almost simultaneoulsy. Some of the symptoms include dyspneoa, pedal oedema, fatigue, dyspnoea on exertion, orthopnoea, paroxysmal nocturnal dyspneoa, cough, nausea, palpitations and weight gain (Gallagher *et al.* 2012).

4.2 Etiology

NHFA (2012), has listed the following conditions as the major causes of HF: hypertension (54%), ischemic heart disease (IHD) (46%), myocardial infarction (MI) (31%), valvular heart disease (22%), diabetes (31%) and renal impairment (26%).

4.2.1 HYPERTENSION

Hypertension causes the increase in sympathetic tone which subsequently causes peripheral vasoconstriction and the release of noradrenaline from the adrenal glands. Renal blood flow is impaired due to activation of the renal efferent sympathetics. The renal sympathetic nervous system causes the reabsorption of sodium ions with release of renin. This triggers the renin-angiotensin-aldosterone pathway (RAAS) and further constrict the vessels leading

to severe damage (Elliott, Bakris & Black, 2004). The total peripheral resistance is increased in hypertensive state, thus leading to increase afterload and the left ventricle often compensate by forming a concentric hypertrophy but this is short lived and the heart will eventually fails (Beevers, Lip & O'Brien, 2007).

4.2.2 ISCHEMIC HEART DISEASE (IHD)

This is caused by the deposition of lipid molecules on the endothelium of the vessels thereby narrowing the lumen and altering its function. This condition usually deprives the myocardium the required amount of oxygen and nutrients. Prolonged reduction in the coronary blood flow will result in regional necrosis of the affected part leading to ventricular failure (Digirolamo and Schlant, 1978).

4.2.3 MYOCARDIAL INFARCTION (MI)

Infarction of the myocardium ensues when an emboli occludes an artery supplying the heart wall with a resultant necrosis of the affected part (Robbins, Cotran & Kumar, 1984). As a result more work is expected from the unaffected myocardium during systole in other to meet up with systemic output (Khan, 2006). In the affected part there is loss of myocardial cell function, myocardial fibrosis, and left ventricular (LV) remodelling. Following this, the LV enlarges triggering the activation of the RAAS in order to compensate for decrease cardiac output but this development further causes the heart to deteriorate (Heart Failure Society of America (HFSA), 2010).

4.2.4 VALVULAR DISEASE/ DYSFUNCTION

In cardiac valve disease, aortic stenosis raises the resistance in the left ventricle leading to increase in pressure afterload which in turn results in left ventricular hypertrophy (concentric hypertrophy) as a compensation for the narrowed aortic opening. The end-diastolic pressure is increased and LV poor perfusion with LV dysfunction ensues (Khan, 2006).

4.2.5 DIABETES MELLITUS AND RENAL FAILURE

In diabetes, there is increased risk for endothelial dysfunction which predisposes the individual to clot formation and arteriosclerosis development. Studies have shown that high blood sugar attenuates the effect of NO (nitric oxide) which is an endothelium derived vasodilator while upgrading the activities of vasoconstrictors such as prostanoid and endothelin; these molecules in turn lead to increase in peripheral resistance (Creager,

Luscher, Cosentino & Beckman,2003). In addition, hyperinsulinemia has been put forward to increase the amount of sodium and water resorption in the distal tubules and this leads to a rise in intracellular sodium and calcium ions in vascular smooth muscle cells resulting to increased contractile ability on the background of pre-existing raised peripheral resistance (TPR) (Williams & Pick-up, 2004). The ability of the kidneys to excrete waste products is impaired in conditions like the renal failure leading to the accumulation of not only nitrogenous substance in the body but also sodium and fluid (Tuttle & Hall, 1978). Renal failure accounts for approximately a third of HF in the UK between 2011 and 2012 (NHFA, 2012).

4.3 CLASSIFICATION AND STAGES OF HEART FAILURE

According to the New York Heart Association Functional Classification (NYHA):

I. Patients with cardiac problems which does not result to any limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea or angina pain.

II. Patients with heart problem which is causing slight limitation of physical activity. But they are comfortable at rest. Ordinary physical activity will result in fatigue, palpitation, angina pain and dyspnoea.

III. Patients with heart problem which causes marked limitation of physical activity. These people are also comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnoea or angina pain.

IV. Patients with cardiac disease resulting in the inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the angina syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased (Francis, Wilson Tang & Sonnenblick, 2004).

4.4 PATHOPHYSIOLOGY

There are two main forms of HF (HF with preserved ejection fraction; HFPEF and HF with reduced ejection fraction; HFREF) (Pearse & Cowie, 2014). HFPEF can be a difficult diagnosis to reach, however, epidemiological studies reveal that approximately 50% of HF patients have preserved EF. In HFPEF (diastolic heart failure), there is diastolic dysfunction leading to concentric hypertrophy as a way of compensating for the condition. This is common with hypertensive heart disease and often occur among elderly females. Conversely, HFREF (systolic HF) occurs when a disease process has occurred in a part of the myocardium (e.g. MI) or the myocardium is generally affected (e.g. dilated cardiomyopathy). The outcome is a heart which is filling well during diastole but is unable to contract efficiently during systole to eject the required volume of blood. This leads to an increase in cardiac size and stretching of the myocardium in accordance with Starling's law to initially increase cardiac output. However, this compensatory mechanism does eventually fail and the cardiac output gradually deteriorates with left ventricular enlargement. The end-result of either HFPEF or HFREF is a reduction in cardiac output which will lead to poor perfusion of organs and subsequently trigger a complex neuro-humoral response (Pearse & Cowie, 2014; Nanayakkara & Kaye, 2015).

4.5 PATHOGENESIS OF SIGNS AND SYMPTOMS

When the heart fails to pump a sufficient volume of blood as a result of any of the above mentioned aetiologies, the kidney usually detect such anomaly as hypo-perfusion and this will trigger the activation of the sympathetic system. Adrenaline and nor-adrenaline would be released subsequently to act on the myocardium increasing its contractility but the effect is short-lived. The RAAS pathway is simultaneously activated to increase sodium ion and water re-absorption which aims to restore the intravascular volume whereas vasoconstriction is also induced via angiotensin II to improve venous return. However, these protective mechanisms are not sustained for too long and the heart eventually fails (Francis, Wilson Tang & Sonnenblick, 2004). According to Khan (2006), when the heart is unable to pump out the blood that flows into its chambers this causes stasis of blood in the vessels. The pulmonary veins become engorged and water and sodium ion begins to leak out in the pulmonary bed causing dyspnoea, orthopnoea and frothy sputum. This also results in hypo-

perfusion of skeletal muscles worsened by the pre-existing vasoconstriction, patients become easily fatigued. The engorged veins continue to leak out fluids in the legs, abdomen and further reduces the quality of life, physical activity and exercise tolerance.

During this condition, there is altered redox state in the vascular bed leading to overproduction of reactive oxygen species. The neuro-humoral pathway is activated, myocardium releases inflammatory mediators and alteration of local shear stress lead to further production of free oxygen radicals and reduction in nitric oxide (NO). This creates imbalance in the functional ability of the blood vessels and the resulting endothelial dysfunction triggers the release of cytokines, uncoupling of nitric oxide synthetase (eNOS); which further deteriorates the heart and advances the progression in HF (Deanfield, Halcox, & Rabelink, 2007). Increase in afterload is noted following rise in systemic and pulmonary vascular constriction; vasomotor dysregulation gradually develops in the kidneys and together with the endothelial dysfunction in the coronary vessels the heart continues to worsen. The endothelium-dependent vasodilatation in the coronary vessels, for example, are impaired worsening coronary blood flow and ventricular function. NO imbalances negatively affects the matrix metalloproteinase production which alters cell migration, cardiac hypertrophy and atherosclerotic plaque instability. Endothelin-1 rises sharply and this causes increased vascular resistance, smooth muscle cell growth, and matrix production leading to vascular remodelling, endothelial dysfunction and HF progression. Reduced amount of NO in HF affects the endothelial progenitor cells, disabling endothelial repair or regeneration. Furthermore, circulating cytokines, for instance the tumour necrosis factor (α-TNF) causes the down regulation of eNOS which further damages the heart and blood vessels (Marti *et al.* 2012)

5.0 PHARMACOTHERAPY

Although mortality rates from HF are high, a number of pharmacological interventions have proven to be beneficial. Angiotensin Converting Enzyme inhibitor (ACEi) and beta-blockers reduces mortality and it is recommended for all patients except in cases where they are contraindicated (NICE, 2010). For instance, where ACEi are not well tolerated, angiotensin

receptor blockers (ARB) may be used. While individuals with complications such as fluid overload are likely to benefit from diuretics, those receiving aldosterone antagonist and vasodilators have shown significant reduction in mortality (Chavey *et al*. 2008).

5.1 ACEi

According to NICE clinical guidelines (2010), the (ACEi) is the common drug of choice in the management of HF. There are evidence that more than two-third of patients have been discharged on ACEi in the UK hospitals between 2011 and 2012 with the figures for men and women nearing 85% and 83% respectively (NHFA, 2012). Research has shown that these medication competitively blocks the Angiotensin Converting Enzyme (ACE) which is a membrane bound enzyme on the vascular endothelium. This subsequently prevents the conversion of angiotensin I to angiotensin II, which is a more potent vasoconstrictor implicated in the pathogenesis of HF (Richardson, 2007). By this action, they interrupt the RAAS pathway which is unusually active in HF. In addition they cause sodium to be excreted by inhibiting the action of aldosterone and also reduce the direct effect of angiotensin II on reabsorption of sodium and bicarbonate in the proximal convoluted tubules (Rang, Dale, Ritter, Flower, & Henderson, 2012). Their vasodilatation properties is further enhanced with the release of endogenous prostaglandins and nitric oxide from the vascular endothelium (Feldman, 2009).

5.2 ARB

These group of medication are often co-prescribed with ACEi in the management of HF and are particularly useful for patients who cannot tolerate ACEi. They act by blocking the angiotensin receptors thus improving exercise tolerance, reducing blood pressure and noradrenaline concentration in the blood (Feldman, 2009).

5.3 Beta-blockers

These drugs are very effective in reducing the level of circulating catecholamine, whose action on the myocardial cells can be deleterious. Beta blockers improve heart muscles contractility and also reduces much oxygen demand (Feldman, 2009). Clinicians have also been warned to start with a low dose and then progress gradually while assessing the heart rate and the blood pressure (NICE, 2010).

5.4 Aldosterone receptor agonist

Aldosterone is increased in HF and often is associated with increased mortality. They act on the mineralocorticoids receptors thereby causing sodium and water retention, production of cytokines, vasoconstriction and myocardial cell as a result of increased production of inflammatory mediators. Aldosterone also causes fibroblast growth and platelet aggregation. This group of drugs act by preventing these events in HF (Feldman, 2009).

5.5 Vasodilators

This include the nitrates and hydralazine group of medications. Hydralazine reduces afterload by acting on the smooth muscles on the arterial wall while nitrates effect their vasodilation property on the veins thereby reducing pre-load on the heart. Thus decreasing venous return, cardiac output and pulmonary resistance (Oglive, 2007; Lejemtel, Sonnenblick & Frishman, 2004).

5.6 Diuretics

These group of drugs are said to have the highest natriuretic efficiency of filtered sodium load and works by inhibiting the reabsorption of sodium ion and water from the thick ascending loop of the kidneys. This region of the nephron contains more sodium chloride channels which makes for intravascular volume and blood pressure reduction (Richardson, 2007).

6.0 EXERCISE INTERVENTION

Data from cardiac rehabilitation programmes (CRP) has shown decrease in morbidity and mortality after MI, coronary artery bypass surgery, percutaneous coronary intervention, cardiac transplantation or valve repair in patients with heart failure. There is an overwhelming evidence that CR halves the cost of re-admission, improves quality of life, functional capacity and so remains one of the most clinically efficient and cost effective approach, in terms of managing cardiovascular diseases (British Association of Cardiovascular Prevention and Rehabilitation (BACPR), 2012). Those who participated in CRP have shown significant reduction in symptoms. Aerobic training is highly advocated, although other activities such as strength training, flexibility, stretching and balance exercises are also encouraged to help improve muscular health and strength. Nevertheless it has been shown, the mode of exercise notwithstanding, that interval training confers greater advantage compared to continuous type of exercises for HF patients. There is a growing evidence that

exercise intensity could be more vital than the duration of training and several methods have been proposed to calculate it. In general, depending on an individual's aerobic capacity and other co-morbidity the duration can vary from the recommended 20 minutes 3 times per week for high intensity aerobic training to 30 - 40 minutes per day if moderate exercise is performed. Also 5 - 10 minutes period of warm-up and cool down must be included before and after each exercise (Perez-Terzic, 2012). Several factors should be considered prior to exercise and the training could be discontinued in the presence of any of these conditions:

TABLE 2. **CONTRAINDICATION TO EXERCISE TRAINING IN HF**
(Asrar, Goy, Levinger, Wong & Hare, 2015).

ABSOLUTE CONTRAINDICATION	RELATIVE CONTRAINDICATION
Progressive worsening of exercise tolerance or dyspnoea at rest	>2kg increase in body mass over previous 1-3 days exertion over previous 3-5 days
Significant ischemia at low exercise intensities (< 2MET)	Concurrent continuous or intermittent dobutamine therapy
Uncontrolled diabetes	Decrease in systolic blood pressure with exercise
Acute systemic illness or fever	New York heart Association Functional class IV
Recent embolism	Complex ventricular arrhythmia at rest or appearing with exertion
Thrombophlebitis	Supine resting heart rate > 100 beat per min
Active pericarditis or myocarditis	Pre-existing co-morbidities
Severe aortic stenosis	Moderate aortic stenosis

MET, metabolic equivalent

The first scientific work concerning the benefits of work-associated exercise training (ET) was published by Morris and colleagues in 1953, who looked into the incidence of coronary artery disease (CAD) among London bus drivers. Their study showed that the incidence was higher among the sedentary bus drivers compared to the conductors. Subsequent studies have

continue to buttress the view that cardiovascular disease (CVD) is less likely among the physically active individuals. A recent meta-analysis showed that physical activity is associated with a marked reduction (35% reduction) in CVD risk and 33% risk reduction in all causes of mortality. In fact, exercise capacity is inversely proportional to risk of CVD and all causes of mortality, even after taking into consideration all cofounding variables. As a result of these outstanding evidence all the major CVD societies made exercise a basic component of health care management especially in the prevention of CVD, recommending at least 30 minutes of moderate intensity exercise 3 to 7 days a week (Adams & Niebauer, 2015).

There are varied opinion on the type of exercise programme and level of intensity considered appropriate for HF patients. On clinical basis, intensity of 70 – 80% of peak heart rate (HR) is usually preferred when using a symptom-limited exercise protocol (Asrar, Goy, Levinger, Wong & Hare, 2015). Nevertheless, the submaximal exercise intensities seem to offer better safety and the most recent Australian guidelines recommended the use of 40 to 70% $\dot{V}O_2max$ with graded increment during the exercise starting from 10 to 15 minutes and increasing to 45 to 60 minutes per session. Various studies have looked into the added benefits of higher intensities when compared to moderate or low intensities and outcome suggest that exercising at higher intensity has better effect on $\dot{V}O_2max$, left ventricular (LV) remodelling, endothelial function and mitochondrial function. Aerobic training has remained the preferred mode of exercise for HF patients; however, resistance training has also shown to have beneficial effect on muscle power, endurance and peripheral blood flow. A research which looked into resistance training versus usual physical activity in HF patients found a modest improvement in ejection fraction (EF) although there was no change in LV volume. In addition, a recent systematic review which examined the effect of resistance training alone or as an adjunct to aerobic training (AT) for improving cardiac function in HF patient also showed that resistance training improved six-minute walk distance compared to no training at all (Asrar Ul Haq, Goy, Levinger, Wong & Hare, 2015).

Another study has examined the impact of combined aerobic and resistance training (ART) versus aerobic training alone in individuals with type 2 diabetes. During this research, a total of 47 participants were randomly assigned to aerobic (27) and ART (20) training group. After training result showed that both test improved body weight. However, the mean arterial blood pressure and endothelin-1 decreased after AT but increased after ART. It was also observed

that adiponectin levels rose by 54% after AT while it decreased by 13% after ART. Matrix metalloprotinease-2, tumour necrosis factor-alpha and monocytes chemo attractant protein-1 levels significantly decreased after AT while it increased in ART. This study suggest that ART, as compared with AT, do enhance body weight reduction, however, it has less effect on insulin sensitivity and endothelial factors, adipokines and proinflammmatory makers released (Lucotti *et al.* 2011). Further studies have compared the impact of moderate continuous training (MCT) at 70% of peak HR and aerobic interval training (AIT) at 90% of peak HR in 27 elderly (>70years) patients who were randomly assigned to three groups after a stable post-myocardial HF. The training was 3 times per week for 12 weeks and the findings of this study showed that AIT was superior to MCT with regards to reversing LV remodelling, aerobic capacity, endothelial function and quality. It showed that high intensity training when compared to an individual's maximum oxygen capacity is more profitable even in the older subjects (Wisloff *et al*. 2007).

7.0 CONCLUSION

In summary, there is no exact direction on the preferred mode of exercise for HF patients, however combined resistance and cardiovascular exercises may likely offer beneficial effect as they would both act centrally and peripherally.

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SYSTEMATIC REVIEW

9.0 ABSTRACT

9.1 BACKGROUND

Flow mediated dilatation (FMD) is attenuated in Heart failure (HF) and this leads to worsening of symptoms. In Europe, the number of HF patients is estimated to be approximately 15 million and that number is set to rise due to ageing of the population. A research conducted between 1999 and 2000, showed that mortality rate was 50% in males and 46% in female within 5 years after the diagnosis of HF. It is estimated that 50% die within four years whereas the other 50% do not survive beyond the first year after diagnosis. Endothelial dysfunction has been implicated in disease progression, however, it is known that increase in physical activity improves and corrects endothelial dysfunction.

9.2 OBJECTIVES

The aim of this systematic review is to examine (i) the effect of exercise modalities (aerobic, strength or combined) on FMD in HF and (ii) to determine which modality confers the greatest benefit and to what extent.

9.3 METHOD

The following databases (MEDLINE, Cochrane library, PubMed, science direct,) were searched for sources that met the inclusion criteria such as (i) randomized controlled trials of

exercise with non-exercise, routine care or sedentary lifestyle. (ii) Duration of the exercise should be at least 2 weeks (iii) age of participant should not be below 18 years. (iv) Endothelial function as measured by FMD before and after the intervention.

9.4 RESULTS

14 studies were included in this review with a total of 583 participants predominantly with reduced ejection fraction (<40%) and New York Heart Association II and III. Compared with control, there were significant improvement ($p< 0.005$) in endothelial function as measured by FMD in the exercise group across all the studies involving HF with reduced ejection fraction (HFREF). Aerobic exercise at a moderate intensity resulted in significant increase in FMD in 12 studies but higher outcome were noted when it was performed in combination with resistance training at a higher intensity. Conversely, one study done among HF with preserved ejection fraction (HFPEF) did not show any significant improvement.

9.5 CONCLUSION

Exercise training is effective in correcting the prevailing endothelial dysfunction common with HF. Combination of aerobic and resistance training as against only aerobic at moderate to high intensity offers the greatest benefit.

10.0 INTRODUCTION

The term endothelial dysfunction often refers to a variety of pathologies including altered anti-inflammatory and anti-coagulant properties of the endothelium, impaired regulation of vascular growth, and abnormality in vascular remodelling. However, in this review it has been majorly used to describe dysregulation in endothelium-dependent vasodilatation commonly associated with the absence of nitric oxide (NO) ubiquity on the vascular wall (Cai & Harrison, 2000). Endothelial dysfunction, typically characteristic of atherosclerotic vessels, has shown to impact negatively on HF patients (Lima de Melo Ghisi, Durieux, Pinho & Benetti, 2000). There is a large body of evidence suggesting the attenuation of NO in heart failure and this has been implicated in disease progression (Katz *et al.* 2004).NO is needed for vascular endothelial growth factor (VEGF) –induced angiogenesis and its absence may be the reason for the reduced capillary density of cardiac muscles, a condition which have been shown to result to cardiomyopathy (Giordano *et al*. 2001). In addition to its anti-thrombotic property, NO is thought to maintain the peripheral vessels in a patent state, thereby reducing afterload on the heart, especially in conditions such as CHF. Accumulating evidence suggest that the absence of endothelium derived NO contributes to the abnormal vasoreactivity response commonly reported in CHF both in the coronary and peripheral vasculature. As a result, chances are that the progression and increased mortality outcome from CHF may be closely connected to the state of the vascular endothelium (Fischer *et al.* 2004).

Flow-mediated dilation (FMD), a term which describes the vasodilatation induced by speed of blood flow, strongly correlates with invasive testing of coronary endothelial function (Dean, Libonati, Madonna, Ratcliffe, & Margulies, 2011; Raitakari & Celermajer, 2000). Endothelial function as evaluated by FMD is a reliable and commonly applied method of evaluating the endothelial integrity. FMD is considered as the vasodilatation induced in response to a sudden increase in shear stress; as a result, is an effective direct marker of vasoreactivity (Gori *et al.* 2011). It is associated with regulation of arterial diameter with increase in blood flow physiologically triggering the release of NO. However, impairment of this function is very common in certain pathological states and peripheral vascular endothelial dysfunction has been frequently reported in HF and is an important indication for prognosis (Dean, Libonati, Madonna, Ratcliffe, & Margulies, 2011).

The beneficial effect of exercise training on endothelial function has been documented. Recent studies have demonstrated that exercise leads to a significant rise in endothelial NOS, which is a precursor to NO. Furthermore, physical activity is known to activate the release of extracellular superoxide dismutase which also contributes to increase level of NO. In addition, NO is also known to attenuate the effect of platelet aggregation and possesses anti-oxidant, anti-proliferative and anti-apoptotic properties (Lima de Melo Ghisi, Durieux, Pinho & Benetti, 2000). Although several pharmacologic therapy has shown to improve endothelial dysfunction, various studies have supported the effective role of exercise in this respect.

Therefore, the aim of this section is to investigate:

1. How the different exercise modalities may affect the endothelium in HF patients?
2. To identify which modality confers the greatest benefit and whether these effect is similar for both preserved ejection fraction and reduced ejection fraction?

11.0 METHODOLOGY

11.1 Search strategy

The Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) statement was the pattern of choice upon which this systematic review was developed and structured (Moher, Liberati, Tetzlaff, Altman, & Prisma Group, 2009).

11.2 Data sources and search

A wide range of databases were searched, as these databases were easily accessible either through the University of Chester portal or via online. Initial search showed that the earliest study on the impact of exercise on vascular function may have been conducted as far back as 1986 (Lejemtel, Maskin, Lucido, & Chadwick, 1986). Therefore, bibliographical databases were searched for relevant studies from 1986 up to mid-August 2015. In order to avoid irrelevant outcomes, searches were restricted to only human studies, young adults were excluded (below 40 years) and participant must have been diagnosed to have heart failure (NYHA I-IV) prior to the intervention.

Studies included were obtained by two main route. First, a detailed search for randomised control studies/trials in some relevant databases to clinical exercise such as: science direct, Entrez PubMed, Scopus, Medline, the Cochrane database of Systematic Review, the Cochrane Central Register of Controlled Trial (CENTRAL) and the University library search website was undertaken. The Cochrane library, ProQuest, Sport discus and (Cumulative index to nursing and allied health literature) CINAHL were also searched to identify all possible related studies.

The titles of the research papers were used initially in finding relevant articles and the Medical Subject headings (MeSH) “exercise training” and “heart failure” were keywords used alone and in combination with other words like “aerobic exercise”, “resistance

exercise", "physical activity", "physical training", "strength training", "exercise training", "exercise", "endothelial function", "endothelial dysfunction", "flow-mediated dilatation", "vascular reactivity", "chronic heart failure", "congestive heart failure".

Searches were made with high sensitivity although there is the likelihood of this reducing precision. Numerous and unnecessary combinations of ideas were avoided while the use of a wide range of search terms were frequently applied with the aid of the Boolean operators such as "AND", "OR", "NOT" or "AND NOT" to enable a more thorough search outcome. Since it is imperative that systematic reviews take a pattern for its search strategy which should reflect consistency and coherency throughout the research; a relevant search strategy was subsequently designed to be able to identify all related studies within the inclusion criteria and as such reduce bias towards studies which may show significant outcome; thus avoid the risk of overestimation of the intervention effect (Centre for reviews and dissemination, 2009; Ryan, Hill, Prictor, & McKenzie, 2013).

This systematic review has been conducted as part of MSc dissertation and so a single reviewer has seen through the whole process.

11.2.1 Minimising the risk of bias

The Cochrane collaboration tool for assessing risk of bias was used to evaluate the studies included in this review (Ryan, Hill, Prictor, & McKenzie, 2013).

11.2.2 Grey literature searches

Grey literature are often referred to as those studies that are not formally published in journals or books.

11.2.3 Hand searched articles

Studies were also hand searched in addition to accessing the above mentioned database in order to maximise the number of studies retrieved and used in this systematic review. Journals were individually searched for articles that assessed the impact of exercise on the

endothelial function in heart failure patients in a randomized controlled trial setting. The online version of these journals that were looked into:

British Heart journal
The journal of the American Medical Association (JAMA)
American Heart Journal
Circulation
European heart journal
Heart
The American journal of cardiology
Cardiovascular prevention rehabilitation
Archives of internal Medicine
The lancet
The New England journal of medicine
Archives of physical medicine and rehabilitation

During the second phase, the reference list on the individual studies were used to conduct a more detailed search. Randomized controlled trials were identified and studies that grouped participant into "exercise only" or used additional intervention to access the endothelial reactivity was eligible to be included in this review. All studies were accessed free online through University of Chester online IBIS learning resource facility.

11.3 SELECTION CRITERIA

In order to improve the quality of studies included, certain eligibility criteria (table 3) were considered a pre-requisite. An initial eligibility criteria was cautiously applied which included more studies so as to avoid leaving out any relevant study.

Table 3. **Initial eligibility screening criteria**

PICOS CONCEPT	Inclusion / Exclusion
Study design	Was the study RCT? Was it a primary research?
Population	Were human subject included? Were the subject over 18 years? Were the subjects diagnosed of HF?
Intervention training or both.	Did the study use aerobic or resistance Was the intervention after the diagnosis?

After the initial eligibility screening, the full text of the studies were gotten from; freely available sources, subscription held by the University of Chester library, and when not available from the above sources then application was made through the University of Chester Library for an inter-library loan.

All the full text studies were examined with the full eligibility criteria (table 4).

Table 4**.** **Full eligibility screening criteria**

PICOS	Inclusion criteria	Exclusion criteria
Study Design	• Was the study fully published? • Was the study published in English Language?	• Studies in Non-English language • Studies that published abstract only.
	• Was the study a primary research? • Was the study a RCT? • Did the study last up to two weeks?	•Review articles, news items, proposed studies, other study design apart from RCT, editorials and letters.

Outcome:	• Did the study include EF? • Did the study include EF data pre and post exercise?	• EF not specified • EF pre and post exercise not mentioned?
Population:	• Did the study include only human subject? • Did the study include adults (>18 years) • Did the study include heart failure patients? • Did the study specify the stage of HF?	• Non HF patients • If the stage of HF was not reported.
Comparators:	• Were the controls HF patients? AND • Were the controls assigned to the Usual care? OR Required to maintain a usual level of exercise? OR asked not to exercise at all? Were control assigned to placebo exercise with mild effect on EF.	•Non HF patients controls •HF control who were assigned to placebo exercise with > moderate effect on EF.
Intervention:	•Was the intervention aerobic or resistance exercise or a combination of both? • Did the exercise take place after the the diagnosis of HF? • Were the details of the exercise, in terms of Frequency, time, intensity, and mode reported? • Did the exercise meet the criteria for high quality training study?	• Exercise intervention with minimal effect on energy expenditure (e.g. yoga, mild stretching etc.) • Exercise interventions which were part of other component (E.g. exercise -diet; exercise-CBT except data for exercise only group is available).

EF = Ejection fraction; HF= Heart failure; CBT = Cognitive behaviour therapy

After the initial screening, it was apparent that abstract only publication would be excluded from the review since they do not provide the level of details required for the study.

11.4 HANDLING DUPLICATION

In order to avoid including studies twice, the specific details of all the studies that met the inclusion criteria were compared one against the other and any duplicate that were identified was treated as a single research but references were made to all the publication in the final review (Centre for Reviews and Dissemination, 2009, p.25; Higgins & Deeks, 2011).

11.5 QUALITY ASSESSEMENT

The importance of assessment of the quality of controlled trials cannot be overemphasized as differences in the quality of the studies may affect the conclusions reached (Armijio Olivo *et al,* 2008). There are mainly three methods which have proven effective in accessing the quality of studies. They include: individual markers, scales and checklist (Jadad *et al*. 1996) (table 3). Scales and Checklist are examples of instrument which can be used to assess the methodological quality of clinical trials. Although both types have been used interchangeably, they are not exactly the same. Both scales and checklist include items which measures quality but the individual responses to scale measurements can be summed up giving an overall overview of the trial quality (Armijio Olivo *et al,* 2008). A number of scales and checklist have been used to asses RCT, however a 5-item scale developed by Jadad and his colleagues is the only known scale develop with a standard scale development technique. Jadad reported that the scores were lower and more consistent if the quality assessment was blinded. However, a study has shown that blinding had no significant effect on Jadad score (Clark *et al.* 1999). Although this scale is a pain-validated tool, which was not designed to check specific details on physical therapy, it is widely used in physical therapy and other related areas (Armijio Olivo *et al,* 2008).

This instrument can be used to measure the likelihood of bias in a research and should not take more than 10 minutes to analysis each study and there is no right or wrong answers (Jadad *et al*, 1999). It could be used by researchers to assess study protocols; by readers and editors of journals to find out research papers that are scientifically authentic. Individuals involved in systematic review or meta-analysis may find it resourceful in performing differential analysis based on the quality of each study included in their review. Patients might find it helpful in evaluating the validity of any evidence presented to them by health professionals (Jadad et al. 1999).

Table 5. **Jadad scale for reporting randomized control trials**

ITEMS	MAXIMUM POINTS	DESCRIPTION	EXAMPLES
Randomization	2	1 point if randomization is mentioned 1 additional point if method of randomization is appropriate Deduct 1 point if method of randomization is inappropriate (minimum = 0).	The patients were randomly assigned into two groups. The randomization was accomplished using computer-generated random number list, coin toss etc. The group assignment was accomplished by alternate assignment, by birthday or hospital number etc.
Blinding	2	1 point if blinding is mentioned 1 additional point if method of blinding is appropriate Deduct one point if the method blinding is inappropriate (minimum = 0)	The trial was conducted in a double blinded manner Use of identical tablets or injectable, or tablets with similar appearance but tastes differently Masking was incomplete
An account of all patients	1	The fate of all patients in the trial is known and where there is no data explanations are given.	40 patient were enrolled in the trial, however 2 in the experimental group and 3 in the control group were discontinued due to break in the protocol

11.6 GUIDELINES FOR ASSESSMENT

11.6.1 Randomization

The method generating the sequence of randomization will be considered appropriate if allows each participant of the study to have equal chance of receiving the same intervention and the investigators could not predict which treatment is next. Methods using date of birth, hospital numbers or alternation to allocate participant should not be considered.

11.6.2 Double blinding

Only on the note that the word "double blind" was used in the study can a study be regarded as double blind. The method will be regarded as appropriate if and only if, it is stated that neither the person doing the assessment and the study participant could identify the intervention being carried out or if in the absence of such statement the use of active placebos, identical placebo or dummies is mentioned.

11.6.3 Withdrawals or dropped out

Participants who were included in the study but who did not complete the observation period or who were not included in the analysis must be described. The number and the reason for the withdrawal in each group must be stated. If there were no withdrawals it should also be stated in the article. If there no statement on withdrawal, this item must be given no points (Jadad *et al.* 1996).

Therefore the Jadad scale may be very useful, quick and easy- to-use tool in the assessment of trials included in the study. For example:

Table 6.

STUDY	**Kobayashi *et al.* 2003**
1 Was the study described as randomized?	1
2 Was the study described as double blind?	0
3 Was there a description of withdrawals or dropped out?	1
4 Was the randomization described as appropriate?	1
5 Was the blinding described as appropriate?	0
Total Jadad score	3/5

The Jadad 5- point's scale was used to evaluate included studies and articles that achieved 3 and above were included in this review so as to reduction the risk of publication selection bias (Jadad *et al.* 1999).

One of the limitations to this scale is its appealing simplicity which may lack empirical evidence (Emerson, 1990; Schulz, 1995b). Since this involves assigning different values to items in the scale, its validity may be difficult to assess. Moreover, it places more emphasis on reporting than the actual process of the trial conduct and as such does not take into consideration one of the most potential bias namely allocation concealment(Juni, 1999). Therefore such scales that measure more of reporting quality like the Jadad scale should not be used to measure methodological quality. Rather the important methodologic components such as concealment of treatment allocation, handling of attrition bias and blinding of the outcome assessment could be identified and assessed individually (Huwiler-Muntener, Juni, Junker & Egger, 2002).

11.7 DATA COLLECTION

The included studies in this review came from a variety of sources. Most of the searches were done in the relevant data bases to extract all possible published or unpublished studies. The search yielded some studies which were compared against the inclusion or exclusion criteria;

moreover the references provided by the search were used to retrieve electronic articles from the University of Chester Library or inter-library loan were necessary.

In addition, a manual search was also conducted while looking through the references of the online results.

11.8 STATISTICAL ANALYSIS

There was no statistical data that was analysed during this study; however, when data were arraigned in a table format to show any change from the baseline information and was depicted with mean ± standard deviation (SD) which is statistically significant ($p < 0.05$).

12.0 RESULTS

12.1 STUDY SELECTION

Studies were included or excluded after comparing them with the PICOS criteria and after full text review, only 14 studies met the inclusion criteria (figure 1).

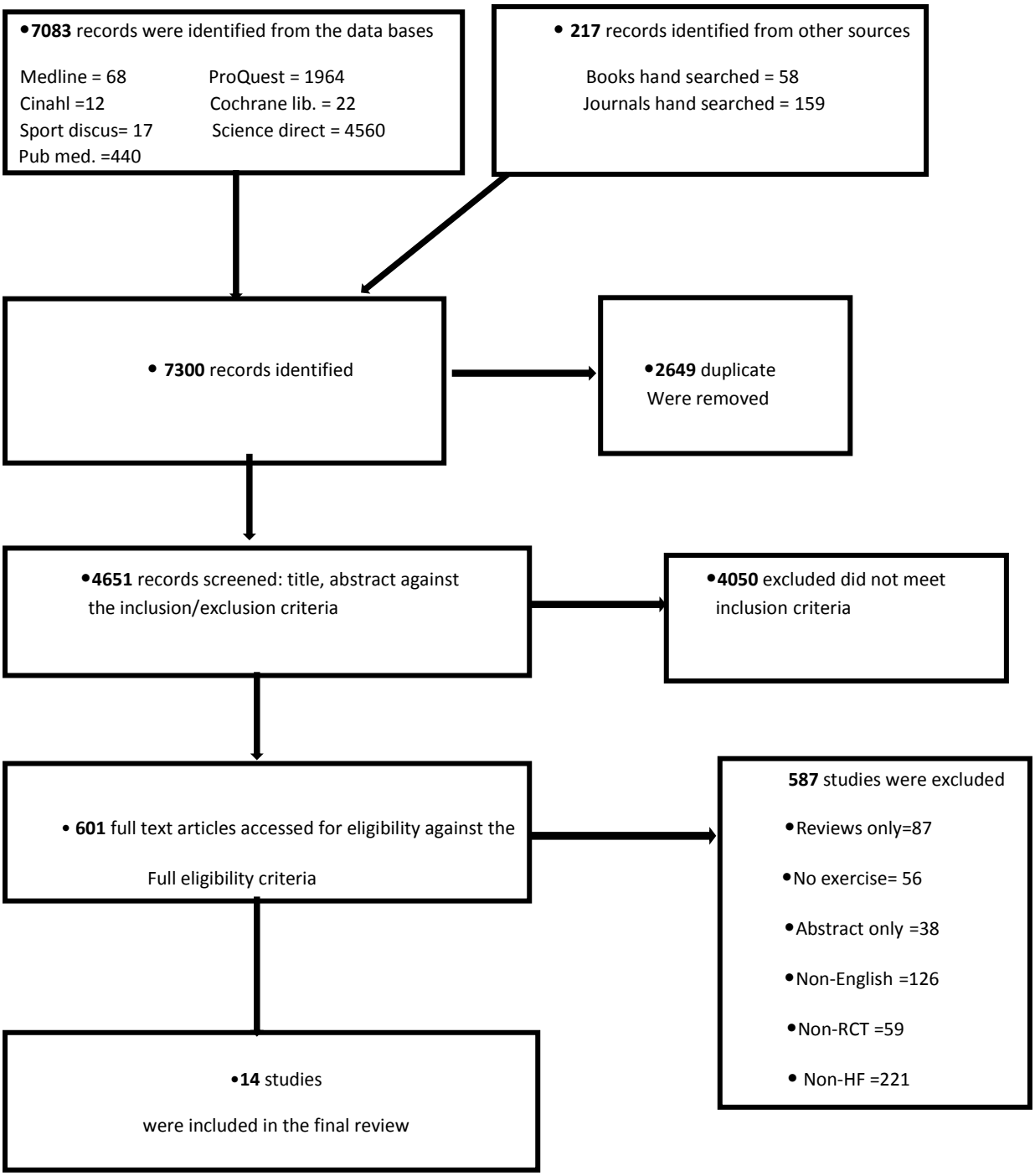

Figure 1. Flow diagram of sequence of data management throughout the review

12.2 GENERAL CHARACTERISTICS

The publication year of the papers included in this review ranges from 1998 to 2015 with most published between 2000 and 2015. They were all written in English language. The studies between 1986 and 1998 did not meet the inclusion criteria. The aim of the studies were to examine the effect of exercise training on the endothelial function in HF patients. Nine out of the 14 studies measured additional variables during their research. One of the studies (Belardinelli *et al*. 2005) determined the impact of exercise on the endothelium of CHF patients with implantable cardioverter defibrillators and cardiac resynchronization therapy whereas another trial (Hambrecht *et al*. 2000) looked at the additive effect of L-arg. to physical activity in correcting endothelial dysfunction in CHF.

12.3 POPULATION CHARACTERISTICS

Eight of the studies were done in European countries like Germany (5 studies), Italy, Greece and Norway (1 study each), USA (2 studies), Australia (2 studies), and two from Japan. The number of participant varied between 20 to 120 individuals with most studies predominantly male subjects. Six out of 14 studies included only male participants in their exercise training and in one study the sex of the subjects were not clearly indicated. All the studies examined elderly (adults) age group and majority of their age were between 41 and 75 years. One study had participants who were above 80 years. Eight studies included female and male in their research others did not.

Most of the participants in the study were in NYHA II or III; and majority of them were expected to be clinically stable prior to exercise the enrolment (table 7).

The total number of participants included in these studies were 583. Of these, 314 were randomised to an exercise programme whereas 269 were in control/comparison group. Only 35 female partook in these studies compared to 426 male subject. The gender for the remaining 120 participants were not indicated (table 7).

12.4 FMD MEASUREMENT

The various studies evaluated FMD mainly by two methods (table 8). 12 studies made use of Ultrasound technique following reactive hyperaemia and 10 out of these underwent supervised cycle ergometry exercise while the other two performed supervised walking on the treadmill. The remaining 2 studies measured FMD using plethysmograph technique and while one of them performed resistance training the other did aerobic exercise.

12.5 STUDY DESIGN

All the 14 studies included in this review where only RCT which had achieved at least 3 score on Jadad scale. In addition, to FMD most of the studies also reported other variables such as (quality of life, peak oxygen consumption, exercise capacity etc.) but only data on endothelial-dependent vasodilatation is reported in this review.

Table 7. Characteristics of included studies

Authors (date)	Participants (Age, Sex, group)	Intervention studied	Type of exercise	Time, Frequency & Duration of each session	Intensity	Outcome(s)
Kobayashi *et al*. 2003	28 CHF (M=20,F=8) Exercise group(55±2)yr. 14(M=12,F=2) Control group (62±2)yr. = 14(M=8, F=6) Exercise group: LVEF : (29±2)% ; Control group: LVEF: (33±2)% NYHA (II – III)	Aerobic Exercise only	Supervised cycle ergometer training	2-3days/wk in two 15 minutes session for 3 months	Used HR at a ventilatory threshold for 15 minutes each session; but if irregular then RPE= 13 (Borg's scale) was used	There was no significant change from baseline values of brachial artery FMD in the HF exercise group (4.34±0.45 vs 4.56 ± 0.43) However, there was a significant increase in FMD in the tibial artery of HF exercise group from their baseline values(3.64± 0.26 vs 6.44 ± 0.56) p<0.01
Parnell *et al*. (2002)	21 CHF (M=19, F=2) Exercise group: 11(M=10, F=1) Control group: 10(M=9, F=1) Exercise group: LVEF: (25± 2)%; Control group: LVEF: (24± 3)% NYHA(II – III)	Aerobic Exercise only	Walking, light hand weights and stationary cycling	Progressed from 30 minutes 3times/wk. to 60 minutes/day for 5-7 days per week for 8 weeks.	50 – 60% maximum heart rate	Significant increase in 6MW test from baseline value (474± 27m to 547±34 m). p=0.008 Decrease in HR was recorded in the exercising group from baseline values (66±3 to 62± 2 beat/min; p= 0.037 but no significant change occurred in the control group. Systemic arterial compliance significantly increased only in the trained group from (0.57± 0.11a.c.u to 0.77± 0.14 a.c.u)
Belardinelli *et al*. 2005	52 CHF (all male) Exercise group: ICD (n=15), ICD +CRT (n=15); Control group: ICD (n=12), ICD +CRT (n=10)	Aerobic Exercise only	Stretching, Supervised electronically braked cycle	Warm up (15min) , braked cycle (40mins), 5mins	60% $\dot{V}O_2max$	The exercise group had significant increase in their endothelium-dependent vasomotor dilatation irrespective of the type of device they received (p< 0.001). Improved QoL, Reduction in LV end-systolic volume index,

	NHYA II (n=29); III(n=23)			loadless recovery for 8 weeks		increase in LV ejection fraction, and decrease in peak early filling velocity were all significant in the trained subjects with CRT.
Bellardinelli *et al*. 2004	59 CHF (all male) Exercise group:(n=30) Control group: (n=29) NYHA II (n=33); (n=26)	Aerobic Exercise only	Supervised cycle ergometry	Warm up (15 min), braked cycle (40min) and 5 min loadless recovery 3times/week for 8 weeks	60% $\dot{V}O_2max$	At 8 weeks the FMD had significantly improved only in the trained subject s from baseline values (2.29±1.13% to 5.04±1.7%).
Linke *et al*. 2001	22 CHF (all male) Exercise group: (n= 11); LVEF:(26±3)% Control group: (n=11) LVEF: (24± 2)% NHYA II (n=16); III (n=6)	Aerobic Exercise only	Supervised electronically braked cycle ergometry	6 times/day for 10 min each over 4 weeks	70% $\dot{V}O_2max$	After 4-weeks of training Ach-mediated, endothelium –dependent vasodilatation significantly increased only in the exercised group (p<0.001). FMD significantly increased from the baseline value (374±57 to 570±76 µm (p<0.01) vs control group at 4 week).
Hambrecht *et al*. 2000	40 CHF (all male) Control group: (n=10) LVEF: (19±3)% ; Exercise group:(n=10)LVEF: (18±3)%; Exercise + L-arg:(n=10) LVEF: (19±3)%; L-arg group:(n=10) LVEF: (18±3)% NHYA II (6); III(34)	Aerobic Exercise and L-arg	Hand grip ergometer training	6 times/day for unspecified period over 4 weeks	70% $\dot{V}O_2max$	After 4- weeks of exercise training, Ach-induced vasodilatation increased four times in exercise group from (2.1±0.1% to 8.6± 0.9%) (p< 0.001)
Selig *et al.* 2004	39 CHF(M=33; F=6) Exercise group:(n=19)	Resistance Exercise only	Hydraulic resistance	5-min warm-up	Moderate intensity	After 3 months of training the FBF significantly improved in response to all 3 levels of

	LVEF: (28 ±7)% Control group: (n=20) NHYA II & III		training: arm &leg cycling ergometers, set of 5-stairs, shoulder press/pull, elbow extension/flexion, knee extension/flexion	& cool down; Upper body 15%,30% & 45% 1RM sessions per week for 3 months		intensities. Control group did not record any significant change
Anagnostakou *et al.* 2011	28 CHF (M=23; F=5) Exercise group 1(interval training): (n=14) LVEF: (36±13)% Exercise group 2(combined): (n=14) LVEF:(39±11)% NYHA I (n=8); II (n=17); III (n=3)	Aerobic OR Combined (Aerobic & Resistance) exercise	Electromagnetically braked cycle ergometer	40 minutes cycle(aerobic) OR 3 Sets of 10-12 Rep with 10 sec. rest in-between for 20 minutes + 20 mins Cycle (combined) Three times a week for 36 sessions	50% of SRT And 55% to 65% of the 2-RM for lower limb and 10-RM for upper limb	After 3 months of rehabilitation, the combined group showed significant improvement in FMD from baseline absolute values of (0.44± 0.24) mm to (0.72± 0.2) mm; whereas interval training group result were not significant.
Erbs *et al*. 2010	37 CHF (all males) NYHA IIIb Exercise group: (n= 18) Control group: (n=19) LVEF: (24±2)%	Aerobic exercise only	Bicycled ergometer and supervised group training (walking,	3 to 6 times per day for 3 weeks followed by home-based 20 to 30 mins	50% $\dot{V}_{O_2}max$	Exercise training for a period of 12 weeks resulted in significant improvement in FMD from (6.1±2.5 to 13.6 ± 2.2) % which correspond to absolute increase in internal diameter of 415± 86µm; In contrast, the control group did not show

			calisthenics and non-competitive ball game)	unsupervised cycle training for 12 weeks; with one supervised group training		any change in FMD.
Hambrecht *et al*. 1998	20 CHF (all males) Exercise group: (n=10) LVEF: (24± 4)% Control group: (n=10) LVEF: (23±3)% NHYA: I &III	Aerobic exercise only	Supervised electronically braked bicycle; Home-based bicycle ergometer and one group training session per week	6 times/day for 10 mins for 3 weeks followed by 2 times/day for 40 mins, 5 days/week for 6 months	70% $\dot{V}_{O_2}$max	After 6 months of aerobic exercise, there was significant improvement in peripheral blood flow from baseline values (1.6± 2.4 to 7.6± 3.4) cm/s ($p< 0.05$ versus control group) at 60µg/min acetylcholine, and from (2.0± 2.0 to 10.9± 3.4) cm/s ($p< 0.05$ versus control group) at 90µg/min acetylcholine.
Wisloff *et al*. 2007	27 (CHF) (M=20; F=7) Exercise group: MCT(n= 9) AIT (n=9) Control group: (n=9) LVEF: <40% NHYA (2.5±0.5)	Aerobic exercise only	"Uphill" treadmill walking	Supervised training 2 times per week: 10mins warm-up; 47 mins training and 3mins cool down and home-based training once every 3 weeks	MCT (70 to 75)% of HR max AIT(90 to 95)% of HRmax Control: 70% of HRmax	At the end of 12 weeks, FMD had significantly increased in AIT group compared to MCT group. Control group did not show any significant change

				Control group: were to follow advice from their doctor; in addition perform 47 mins continuous treadmill walking at 70% of peak HR every 3 weeks		
Sandri *et al*. 2015	60 (CHF) and 60 (RC) Sex =not recorded RC ≤55yrs (n=30) RC ≥65yrs (n=30) CHF≤55yrs(n=30) CHF≥65yrs(n=30) LVEF: <40%	Aerobic exercise only	Supervised bicycle ergometer and one group training session (walking, calisthenics and ball games) Control: usual care	4 times/day 15 to 20 mins for 4 weeks with 5 mins warm-up and cool down for 4 weeks	60 to 70 % $\dot{V}_{O_2}max$	Exercise training resulted in significant increase in FMD among the younger (11.3 ± 2.5% to 15.7± 1.9%) and older CHF patients (10.5± 1.5% to 14.9± 2.2% p<0.05) versus control group.
Kitzman *et al*. 2013	63 (HFPEF) Exercise group: (n= 32) Control group: (n= 31) NHYA II & III LVEF: >50%	Aerobic exercise only	Walking on track and cycle and arm ergometer	10 min (warm-up) Trained from 20 mins to 40 mins 10 min	40 -50% to 70% HRR	After 16 weeks of training, there was no significant change in the FMD in the training group.

				(recovery)		
Ozasa *et al*. 2012	27 (CHF) (M=12), (F=15) Exercise group: MACG: (n=13) C-ET: (n= 14) NYHA II (n=3); III (n= 24) LVEF: 46.0±14.4 %	Aerobic exercise only	Machine-assisted cycling and C -ET	MACG: 20 mins (warm-up) stretching; 15 mins cycling C-ET: 15 mins gait training and 5 mins (cool down) stretching	< 30% HRR	After 2 weeks of training a significant increase in RH-PAT index in MACG was observed from (1.59±0.52 to 1.93± 0.63). No change was seen in C-ET group.

NYHA= New York Heart Association; MACG= Machine-assisted cycling group; C-ET = Conventional training; HRR= Heart rate reserve; RH-PAT = reactive hyperaemia peripheral arterial tonometry; LVEF = Left ventricular ejection fraction; CHF = Chronic heart failure; HFPEF = Heart failure with preserved ejection fraction; FMD = flow-mediated dilatation; RC = Healthy subjects; MCT = Moderate continuous training; AIT= Aerobic interval training; FBF= Forearm blood flow; L-arg. = L-arginine; CRT = Cardiac resynchronization therapy; ICD = implantable cardioverter defibrillator; $\dot{V}O_2max$ = Maximum oxygen capacity; HRmax = maximum heart rate; MW = meter walk; RPE = Rate of perceived exertion..

Table 8. Characteristics of studies included (FMD measurement)

STUDY	How FMD was measured.
Kobayashi *et al*. 2003	Two-dimensional ultrasound
Parnell *et al*. 2002	Non-invasive applanation tonometry and Doppler aortic velocimetry
Belardinelli *et al*. 2005	Ultrasound probe
Bellardinelli *et al*. 2004	Ultrasound probe
Linke *et al*. 2001	High precision ultrasound
Hambrecht *et al*. 2000	Ultrasound and Doppler transducer
Selig *et al.* 2004	Venous occlusion plethysmography
Anagnostakou *et al.* 2011	Doppler ultrasound
Erbs *et al*. 2010	High resolution ultrasound
Hambrecht *et al*. 1998	Doppler guide wire with Doppler ultrasound
Wisloff *et al*. 2007	Ultrasound
Sandri *et al*. 2015	High resolution ultrasound scanning echo-tracking angiometer
Kitzman *et al*. 2013	Bisound phase II ultrasound system
Ozasa *et al*. 2012	Plethysmographic technique

13.0 DISSCUSSION

13.1 VASCULAR EFFECT OF EXERCISE TRAINING

CHF is a complex syndrome which may be characterised by increased vascular resistance due to autonomic and hormonal irregularities. The resulting vicious cycle continues to deteriorate the endothelial vascular integrity and further worsening outcomes (Belardinelli, Lacalaprice, Faccenda, Purcaro & Perna, 2005). This present review however attempts to validate the theory that exercise training improves endothelial-dependent vasodilatation and has been considered as the single most important indicator of endothelial function. Endothelial dysfunction has been proposed to reduce the distensibility of conduit vessels. In CHF patients, endothelium-derived relaxing factor-mediated increase in distensibility are impaired leading to a worse condition for the heart (Ramsey *et al*. 1995). It has been put forward that these peripheral vascular abnormalities could be attenuated in CHF following exercise training. However, the exact mechanism by which this is achieved is not completely understood. Previous studies have shown that systemic arterial compliance improves with regular training, this improvement in the function of the endothelium following exercise training may be the reason behind the increased arterial compliance identified in this research (Parnell, Holst & Kaye, 2002).

Some of the studies included in this review reported a significant but limited improvement in FMD within the exercising extremity. The study by Kobayashi *et al*. (2003) showed that lower-limb dominant exercise training improved FMD in the lower limb but not in the untrained upper limb. Although this study reported significant improvement in EF, vasoconstritive substances and pro-inflammatory humoral factors were left unaltered, raising a high index of suspicion that the reduction in humoral factors such as norepinephrine, endothelin-1 and interleukin-6 may not be the primary pathway of correction of endothelial dysfunction post-exercise. Noris *et al*., (1995) has shown that lamina flow of blood in the human umbilical vein endothelial cells (HUVEC) induces the production of nitric oxide (NO) which is predominantly dependent on the local shear-stress effect. This laminar shear stress at 8 dyne/cm2 also up-regulates the level NO synthase mRNA. In essence, these outcome suggest that local blood flow is responsible for the production of vasodilation substance by the endothelial cells. Conversely, some other studies provide evidence to suggest that the effect of exercise training on the endothelium may not only be limited to the exercising extremity. Belardinelli,

Capestro, Misiani, Scipione & Georgiou (2005) documented significant improvement in endothelium-dependent vasomotor response of brachial artery following a leg exercise (bicycle ergometry); endothelial function improved irrespective of the NYHA functional class of the participants showing the effectiveness of exercise in correcting endothelial dysfunction in HF patients. It is considered that exercise-induced shear stress activates endothelium derived NO synthase with a consequent production in NO and other vasoactive compounds like bradykinin and prostacyclin which tends to improve the vasodilatation properties of the endothelium. In a related study, handgrip exercise showed to have a positive effect on the FMD; however this was only restricted to the exercising forearm, but when bicycle ergometer was used, a systemic cardiovascular effect was observed; indicating that systemic effect is likely when more muscle mass are engaged (Linke *et al*. 2001; Anagnostakou *et al*. 2011). Although it is expected that the greatest increase in pulsatile blood flow should be in the vessels within the exercising muscle, the rise in blood pressure (BP) and heart rate (HR) during exercise increases pulsatile flow in the body systematically; therefore giving rise to improved endothelial-dependent vasodilatation. The result is a vasodilatory response to Ach at the maximum concentration, to rise by 2.5 fold whereas FMD improved by 50% in HF (Linke *et al* 2001). Another study demonstrated a generalized vascular adaptation following a forearm resistance training. They argued that these benefits may not have resulted from just increase in blood flow but also by altering vital haemodynamic parameters (Maiorana *et al.* 2000). These outcomes, however, stands in contradiction to a previous research which failed to show similar result. Research conducted by Demopoulos *et al*. (1997) did not show any significant improvement in endothelial function of the untrained extremity following bicycle ergometer training. However, several explanation has been put forward as reasons for the disparity. Firstly, exercise were conducted at a significantly low intensity which could not raise the blood pressure amplitude to a level that could create a significant systemic effect. Secondly, the participants in Demopoulos *et al.* study were in the advanced stage of their heart condition. Moreover, their FMD were accessed using forearm venous occlusion plethysmography while other studies that showed systemic effect used high resolution ultrasound. Therefore the difference in outcome might have been due to the difference in the methodologic approach.

Another study which examined the impact of exercise on sexual dysfunction showed that improvement in the endothelium-dependent vasodilatation is the strongest independent predictor of sexual activity improvement in men with CHF. The result of the study demonstrates that exercise at a moderate intensity on bicycle ergometer improves endothelium-dependent vasorelaxation of a conduit vessel located in a part of the body that is not directly exercised. This seems to agree with evidence from previous studies suggesting a systemic benefit from a leg exercise (Belardinelli, Lacalaprice, Faccenda, Purcaro & Perna, 2005; Selig *et al*. 2004; Vona *et al*. 2004).

Wisloff *et al*. (2007) showed greater improvement in brachial artery FMD in aerobic interval training compared to moderate continuous training in CHF. The investigators used high intensity aerobic interval training consisting of 4 minutes intervals at 90% to 95% of HRmax separated by 3 minutes of active pauses walking at 50% to 70% HRmax. However, combination of both interval training and strength training has shown to be more significant in terms of improvement in vascular reactivity. It is suggested that this outcome could be as a result of the different protocol applied by this study – a high intensity stimulus together with a higher exercise duration interval and a longer recovery period may be the main reason for the achieved outcome (Anagnostakou *et al*. 2011).

13.2 EFFECT OF COMBINED versus AEROBIC TRAINING ON NO PRODUCTION

Physiologically, the vascular endothelium produces vasoactive compounds such as NO, prostacyclin and bradykinin- which contribute to maintain the patency of the conduit vessels with the aim of ensuring proper flow of blood with a non-adherent endothelial surface (Lima de Melo Ghisi, Durieux, Pinho & Benetti, 2000). A decrease in NO bioavailability often result from reduced expression of endothelial cell NO synthase (eNOS), absence of cofactors or substrates for eNOS, poor activation of eNOS due to signalling problem with endothelial cells and increased production of reactive oxygen species (ROS) which degrades NO (Cai & Harrison, 2000). There is a large body of evidence linking the reduction in NO bioavailability as the main underlying causative factor in endothelial vascular dysregulation. Shear stress has been pointed out as the most effective physiological stimulant for eNOS gene expression and NO availability. In severe chronic heart failure (CHF) there is a decrease in endothelium derived NO and endothelium-dependent vasodilatation as a result of reduced ejection fraction (EF) and peripheral blood flow causing less shear stress to be exerted on the inner surface of the vascular endothelium (Bauersach & Widder, 2008). However, Green *et al*. (2004) indicated that a combination of aerobic and resistance training improves endothelium-dependent NO-mediated vascular function to a greater extent. This is supported by another study which showed that performing aerobic exercise after resistance training resulted in a significance increase in FMD whereas aerobic exercise performed before RT did not significantly improve FMD (Okamoto, Masuhara, & Ikuta, 2007). Evidence from the current review suggest that combined exercise as opposed to only aerobic training appears to be more beneficial to HF patients but to how extent this is true is still subject to further investigation.

14.0 LIMITATIONS TO STUDY

One of the major limitation to these study is that majority of the participants were predominantly male and so the result may be equivocal on its outcome especially when considering how the female counterparts actually gained from these trainings under review. Furthermore, the failure of two of the studies (Sandi *et al*. 2015; Kitzman *et al*. 2013) which had a total of 183 persons (nearly one in three of all participants), to report clearly the gender of its participants, unfortunately leaves the results at the mercy of ambiguity. Another observable flaw to these studies is that none of the research papers provided clear evidence on the sustainability of the improvement in the endothelial function gained after exercise. Raising further speculations on the need to further investigate the long term (12 months or more) outcomes after exercise in HF. Finally, out of the 14 studies included only 2 studies applied resistance training and the reason for this is still unclear. Could it be that the participants were better motivated to undertake aerobic exercise or were they just being cautious in avoiding resistance exercises?

15.0 CONCLUSION

The outcome of this review suggest that different modes of exercise (aerobic, resistance or combined) have significant effect on the FMD. This however depends on the intensity of the exercise program. The most appropriate range may be difficult to determine since HF does not occur in isolation, it is imperative then that the vascular impact of the other co-morbidities be considered also during exercise programming thereby making the likelihood of a universal protocol almost impossible. However, most of the studies that yielded significant outcome performed aerobic exercise at a moderate intensity, although greater outcome were recorded when performed in combination with resistance training and at a higher intensity.

A study has confirmed that vascular endothelial functions are impaired in HFPEF (Marechaux *et al.* 2015). However, results from this review suggest that the improvement in EF occurred mostly with studies done among HFREF, with one study done among HFPEF showing no significant difference, therefore raising a high index of need to further explore the relevance of exercise on the endothelial function especially among HFPEF.

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17.0 APPENDIX

Table 9. **JADAD SCALE FOR THE POTENTIALLY INCLUDED STUDIES**

STUDY	Was the study described as randomised?	Was the study described as double blinded?	Was there a description of withdrawals and dropouts?	Was the randomization described as appropriate?	Was the blinding described as appropriate?	Jadad score
Hornig, Maier & Drexler, 1996	--	--	+	--	--	1/5
Ozasa, Morimoto,Bao,Shio& Kimura, 2012	+	--	+	+	--	3/5
Kobayashi *et al*. 2003	+	--	+	+	--	3/5
Belardinelli *et al*. 2005	+	--	+	+	--	3/5
Bellardinelli *et al*. 2004	+	--	+	+	--	3/5
Linke *et al*. 2001	+	--	+	+	--	3/5
Hambrecht *et al*. 2000	+	--	+	+	--	3/5
Selig *et al.* 2004	+	--	+	+	--	3/5
Anagnostakou *et al.* 2011	+	--	+	+	--	3/5
Erbs *et al*. 2010	+	--	+	+	--	3/5
Hambrecht *et al*. 1998	+	--	+	+	--	3/5
Wisloff *et al*. 2007	+	--	+	+	--	3/5
Sandi *et al*. 2015	+	--	+	+	--	3/5
Kitzman *et al*. 2013	+	--	+	+	--	3/5
Parnell *et al*. 2002	+	--	+	+	--	3/5